Recent advances in inhaled nitric oxide therapy in neonates: A review of the evidence

Inhaled nitric oxide has been used to treat babies with hypoxaemic respiratory failure for over 15 years and there are now a number of randomised controlled trials that have examined the safety and efficacy of this therapy. This article reviews the evidence base and provides a systematic review and meta-analysis of randomised controlled trials of inhaled nitric oxide in term and preterm babies.

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Key points

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1. Inhaled nitric oxide reduces the need for ECMO in term and near-term babies with hypoxaemic respiratory failure.
2. Inhaled nitric oxide may reduce the risk of death and/or bronchopulmonary dysplasia when given as early 'prophylactic' treatment to preterm infants.
3. The optimal dose of inhaled nitric oxide remains uncertain, although doses between 1-20 ppm are most commonly used.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator licensed for the treatment of hypoxic respiratory failure associated with pulmonary hypertension in newborn infants ≥ 34 weeks' gestation. Although the first reports of its use were published in 1991, it only received regulatory approval (a 'licence') for use in term and near-term neonates in the USA in 1999 and in Europe in 2001. In addition, it is frequently used outside the licensed indication ('off-label') in preterm neonates. Since the earliest reports, there have been a number of clinical trials that have investigated the efficacy of iNO therapy in acute and chronic neonatal respiratory disorders. This article reviews the evidence base for use of iNO in clinical practice.

The rationale for iNO therapy

Hypoxaemic respiratory failure in neonates is primarily due to intra-pulmonary shunting and/or ventilation-perfusion mismatch resulting in continued perfusion of air spaces which are inadequately ventilated. In this setting, iNO improves oxygenation by redistributing pulmonary blood flow away from poorly ventilated lung regions to better ventilated lung regions. In a minority of babies, persistent pulmonary hypertension of the newborn (PPHN), a syndrome characterised by high pulmonary vascular resistance, pulmonary hypertension and extra-pulmonary shunting, is the cause of severe hypoxaemia. Treatment with iNO selectively lowers pulmonary vascular resistance and reverses or decreases the extra-pulmonary shunt, thereby improving pulmonary blood flow and oxygenation.

In addition to its potential beneficial effects on gas exchange, iNO has also been shown, in experimental models of lung injury, to have potent anti-inflammatory and anti-oxidant effects; to preserve surfactant function; and to play an important role in pulmonary vascular development. These findings suggest that early treatment may be a useful strategy in minimising lung injury and reducing the risk of developing chronic lung disease in preterm infants.

Overview of randomised controlled trials (RCTs)

In the past decade there have been 27 published RCTs investigating the use of iNO in a total of 4245 newborn babies infants, making it one of the most studied interventions in neonatal medicine.

In this review only trials investigating the medium to long-term efficacy of iNO in term and preterm babies have been selected. Studies that allowed 'back up' iNO therapy, which would have permitted 'contamination' of the control group (where control infants receive the intervention to be studied) and therefore may have potentially diluted the observed effect of iNO therapy, have been excluded. Individual trials also varied in terms of timing, dose and duration of iNO therapy as well as degree of exposure to antenatal steroids and concomitant respiratory treatments. Clearly each of these variables has the potential to influence important clinical outcomes and one should be wary of important differences between trials when interpreting pooled estimates of effects derived from a systematic review and meta-analysis.

Study	N	Population studied	Age at trial entry	Respiratory disease severity at trial entry	Dose/duration of iNO used	Comments
NINOS 1997[1]	235	Infants ≥ 34 weeks' gestational age	< 14 days, mean age = 1.7 days	OI ≥ 25, mean OI = 43-45.1	20-80 ppm for a maximum duration of 14 days, median duration 40 hours	CDH patients excluded; blinded intervention
Roberts 1997[2]	58	Infants ≥ 37 weeks' gestational age and ≥ 2.5 kg	Not specified	PaO_2 ≤ 55 mmHg in FiO_2 1.0 plus echocardiographic evidence of pulmonary hypertension, mean OI 43-46.	10-80 ppm, maximum duration 8.5 days, median 2 days	CDH patients excluded; blinded intervention
Wessel 1997[3]	49	Infants ≥ 34 weeks' gestational age	Median age = 18-25 hours	PaO_2 < 100 mmHg with FiO_2 1.0 plus echocardiographic evidence of PPHN, median OI = 29.4-30.4	5-80 ppm, duration not specified	CDH patients excluded; non-blinded intervention
Davidson 1998[4]	155	Infants ≥ 37 weeks' gestational age and 2.0 kg, or > 2.0 kg and ≥ 39 weeks	< 72 hours, mean age 25-26 hours	PaO_2 40-100 mmHg with FiO_2 1.0 and mean airway pressure ≥ 10 cm H_2O, plus echocardiographic evidence of PPHN, mean OI = 24-25.	5-80 ppm for a maximum duration of 14 days, mean duration 58 hours	CDH patients excluded; blinded intervention
Christou 2000[5]	42	Infants ≥ 34 weeks' gestational age	Median age 21-28 hours (range 4-107 hours)	PaO_2 < 100 mmHg with FiO_2 1.0 plus echocardiographic evidence of pulmonary hypertension; median OI = 30-32	20-40 ppm, median duration 62 hours	CDH patients excluded; non- blinded intervention; > 90% babies treated concurrently with HFOV.
Clark 2000[6]	248	Infants ≥ 34 weeks' gestational age	≤ 4 days, mean age = 28 hours	OI ≥ 25, mean OI = 37-41	5-20 ppm for a maximum duration of 96 hours	CDH patients included; Majority of trial conducted with a blinded intervention
INNOVO 2006[7]	60	Infants ≥ 34 weeks' gestational age	< 28 days, 88% were < 3 days old	'Severe respiratory failure', 37% had OI ≥ 40	5 -20 ppm, duration < 48 hours in 55% of babies	75% received other pulmonary vasodilators; non-blinded intervention; CDH patients included

TABLE 1 Details of randomised controlled trials of iNO in term and near-term babies. Excluding 6 trials where back up treatment with iNO was permitted and 1 trial that exclusively recruited babies with congenital diaphragmatic hernia.

Term and near-term infants (≥ 34 weeks' gestation) without congenital diaphragmatic hernia

A total of 1709 term or near-term babies have been studied in 16 RCTs of iNO therapy. In this review six RCTs which permitted back up iNO therapy, two RCTs that compared different iNO dosing regimes and one RCT that exclusively studied babies with congenital diaphragmatic hernia were excluded. **TABLE 1** summarises the key characteristics of the included trials.

Most studies have demonstrated a short term benefit in terms of oxygenation with iNO therapy. Inhaled nitric oxide reduces the need for extracorporeal membrane oxygenation (ECMO) in term and near-term babies with severe respiratory failure (risk difference -0.20 [95% CI -0.27, -0.14] i.e. treating 5 babies with iNO would prevent one baby requiring ECMO), but there is no evidence of an effect on mortality (**FIGURES 1A and 1B**).

Category	Description	Number of RCTs	References
Early prophylactic treatment	Treatment of babies requiring mechanical ventilation or nasal CPAP < 72 hours of age and at risk of death/BPD, irrespective of severity of respiratory disease	2	12, 13
Early rescue treatment	Treatment of babies with established respiratory failure in the first week of life, based on severity of respiratory disease	5	14-18
Late treatment	Treatment of babies requiring ventilation or nasal CPAP ≥ 72 hours and at risk of death/ BPD, irrespective of severity of respiratory disease	2	19, 20

TABLE 2 Categories of randomised controlled trials. Excluding two trials where back-up treatment with iNO was permitted.

Five RCTs have reported long term neurodevelopmental outcomes[7-11]. Inhaled nitric oxide therapy in term and near-term babies is not associated with an effect on neurodisability, either beneficial or detrimental. Babies treated with iNO appear to have comparable outcomes to those treated without iNO.

Preterm infants (< 34 weeks' gestation)

Eleven RCTs have been published investigating the use of iNO in a total of

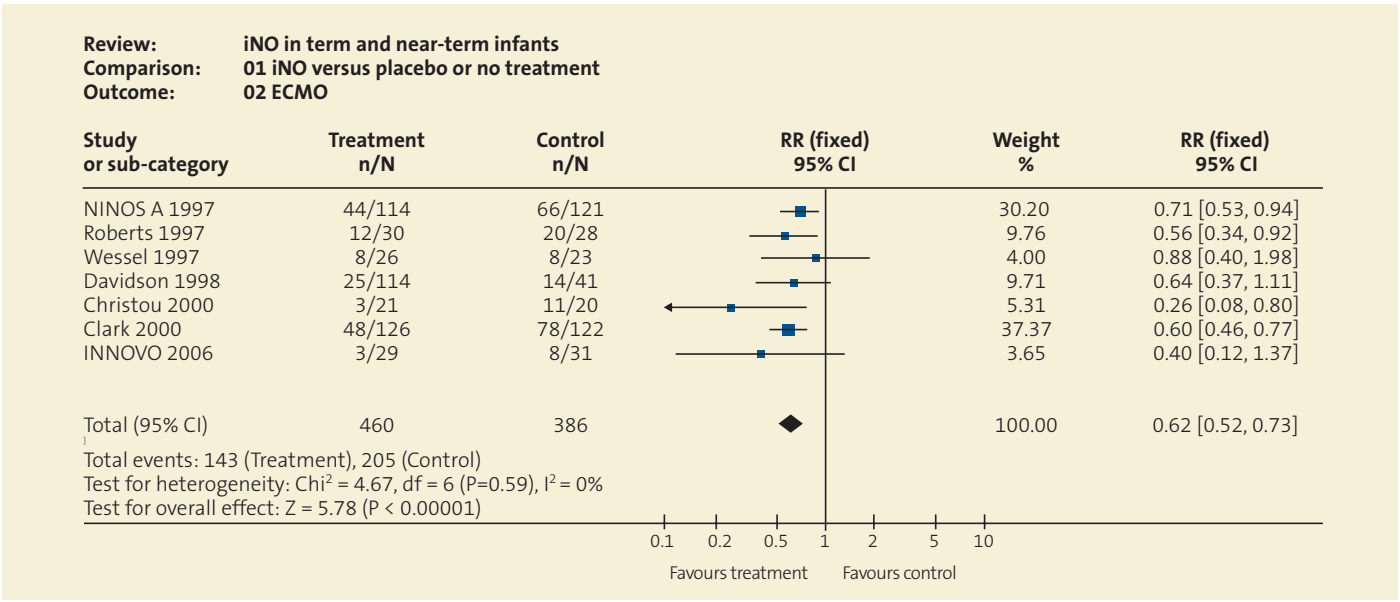


FIGURE 1A Meta-analysis of randomised controlled trials of iNO in term and near-term babies: Effect of iNO therapy on need for ECMO.

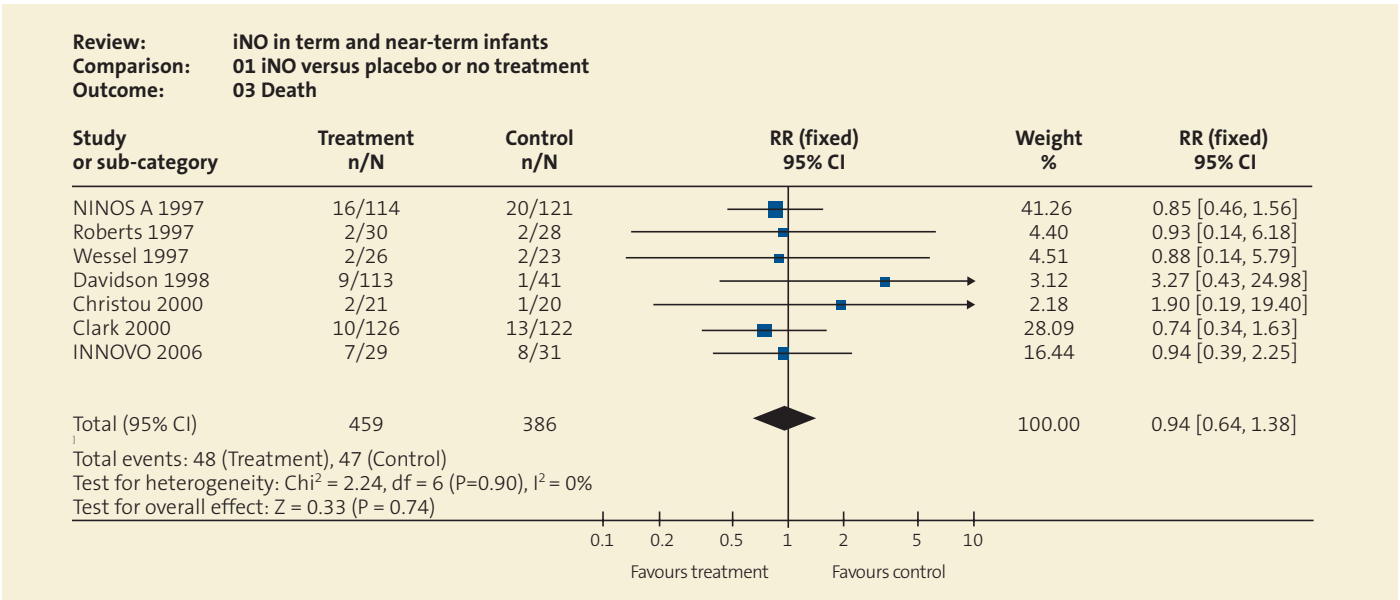


FIGURE 1B Meta-analysis of randomised controlled trials of iNO in term and near-term babies: Effect of iNO therapy on death.

2536 preterm infants. In this review two RCTs which permitted back up iNO therapy have been excluded[12-20]. The key characteristics of included trials are summarised in **TABLES 2 and 3**.

Although many studies have demonstrated convincing evidence of a short term response in oxygenation with iNO therapy, it is medium to long term clinical outcomes which are of greatest relevance to clinicians. **TABLE 4** and **FIGURES 2A-C** provide an overview of the efficacy of iNO therapy with respect to important clinical outcomes in preterm infants categorised by study type.

Two trials have demonstrated that early prophylactic treatment is associated with a reduction in the risk of death and/or bronchopulmonary dysplasia (BPD)[12-13]. The magnitude of effect is such that treating 17 babies with iNO would prevent death and/or BPD in one baby. Sub-group analyses in these trials suggest that iNO may be more effective at reducing the risk of death or BPD in larger preterm infants (≥ 1000 g) and those with milder respiratory disease (OI < 7).

In this meta-analysis, there is no convincing evidence that iNO has a beneficial effect when used as early rescue treatment and late treatment. However, sub-group analyses in individual trials have again suggested that early rescue treatment with iNO may be more effective in larger preterm babies[17], and that late treatment may be more effective when started at 7-14 days as compared to 15-21 days[20].

Early prophylactic treatment with iNO was associated with a reduced risk of severe intraventricular haemorrhage (IVH)/periventricular leukomalacia (PVL) and long term neurodisability in one study[12, 21]. The other study demonstrated increased survival without severe IVH/PVL with iNO therapy[13]. The only other (late treatment) study to report long term outcomes did not demonstrate any long term benefits or harms with iNO therapy[22].

Indications for iNO therapy

Term and near-term infants

Inhaled nitric oxide should be considered as an adjunct to conventional respiratory support in cases of respiratory failure with a severe defect in arterial oxygenation, despite surfactant therapy and optimisation of ventilation. Our practice is to use iNO when the oxygenation index (OI = MAP x FiO_2 x 100/ PaO_2 in mmHg) is greater than 25, with or without

Study	Study type	N	Population studied	Age at trial entry	Respiratory disease severity at trial entry	Dose/duration of iNO used	Comments
Schreiber 2003[12]	Early prophylactic treatment	207	Infants < 34 weeks' gestational age and birth weight < 2000 g	< 72 hours	Ventilated, median OI = 6.8-7.3	5-10 ppm for maximum duration of 7 days	Blinded intervention. Low antenatal steroid exposure; factorial design with infants also randomised to receive HFOV
Kinsella 2006[13]	Early prophylactic treatment	793	Infants < 34 weeks' gestational age	< 48 hours	'Respiratory failure requiring ventilation', mean OI = 5.4 - 5.8	5 ppm for a median duration of 14 (range 0-24) days	Blinded intervention
Kinsella 1999[14]	Early rescue treatment	80	Infants ≤ 34 weeks' gestational age	< 7 days of age, mean age 27-30 hours	Ventilated with a/A < 0.10, mean PaO_2/FiO_2 = 5.6	5 ppm for a maximum of 11 days	Blinded intervention
Srisuparp 2002[15]	Early rescue treatment	34	Infants < 2000 g	< 72 hours	Ventilated with OI > 4-12 depending on birth weight, mean OI = 10.8-11.9	1-20 ppm, maximum duration of 7 days	Non-blinded intervention. Low antenatal steroid exposure
INNOVO 2005[16]	Early rescue treatment	108	Infants < 34 weeks' gestational age	< 48 hours	'Severe respiratory failure' requiring ventilation, median OI = 32	5-40 ppm, duration < 48 hours in 45% of babies	Non-blinded intervention. Frequent use of other vasodilators
Van Meurs 2005[17]	Early rescue treatment	420	Infants < 34 weeks' gestational age	< 5 days, mean age 26-28 hours	Ventilated with OI > 7.5 – 10, mean OI = 22-23	5-10 ppm, maximum duration of 14 days	Blinded intervention
Dani 2006[18]	Early rescue treatment	40	Infants < 30 weeks' gestational age	< 7 days, mean age 43.7 hours	Ventilated with FiO_2 > 0.50 and a/A < 0.15, mean OI = 14.7-18.1	2-10 ppm, median duration 98.5 hours	Non-blinded intervention Low antenatal steroid exposure
Subhedar 1997[19]	Late treatment	42	Infants < 32 weeks' gestational age	> 96 hours	'High risk' of developing BPD using a risk score, median OI 3.9-7.9	5-20 ppm for maximum duration of 72 hours	Non-blinded intervention Factorial design with infants also randomised to receive dexamethasone
Ballard 2006[20]	Late treatment	582	Infants < 1250 g and ≤ 32 weeks' gestational age	7-21 days	Mechanical ventilation or nasal CPAP, median FiO_2 x MAP = 3.5 (ie. mild lung disease at trial entry)	2-20 ppm for a minimum duration of 24 days	Blinded intervention

TABLE 3 Details of randomised controlled trials of iNO in preterm. Excluding two trials where back up treatment with iNO was permitted.

Outcome	RR (95% CI)	ARR 95% CI , NNT	NNT
A) Early prophylactic treatment			
Severe IVH/PVL	0.70 (0.53, 0.91)	- 0.07 (-0.12, -0.02)	14
BPD at 36 weeks	0.92 (0.83, 1.02)		
Death	0.77 (0.61, 0.98)	- 0.06 (- 0.11, -0.01)	17
Death or BPD	0.92 (0.85, 0.99)	- 0.06 (- 0.12, 0)	17
B) Early rescue treatment			
Severe IVH/PVL	1.02 (0.80, 1.31)		
BPD at 36 weeks	0.93 (0.78, 1.09)		
Death	1.05 (0.89, 1.22)		
Death or BPD	0.93 (0.87, 1.00)		
C) Late treatment			
Severe IVH/PVL	No data		
BPD at 36 weeks	0.90 (0.78, 1.04)		
Death	1.06 (0.64, 1.74)		
Death or BPD	0.90 (0.80, 1.02)		

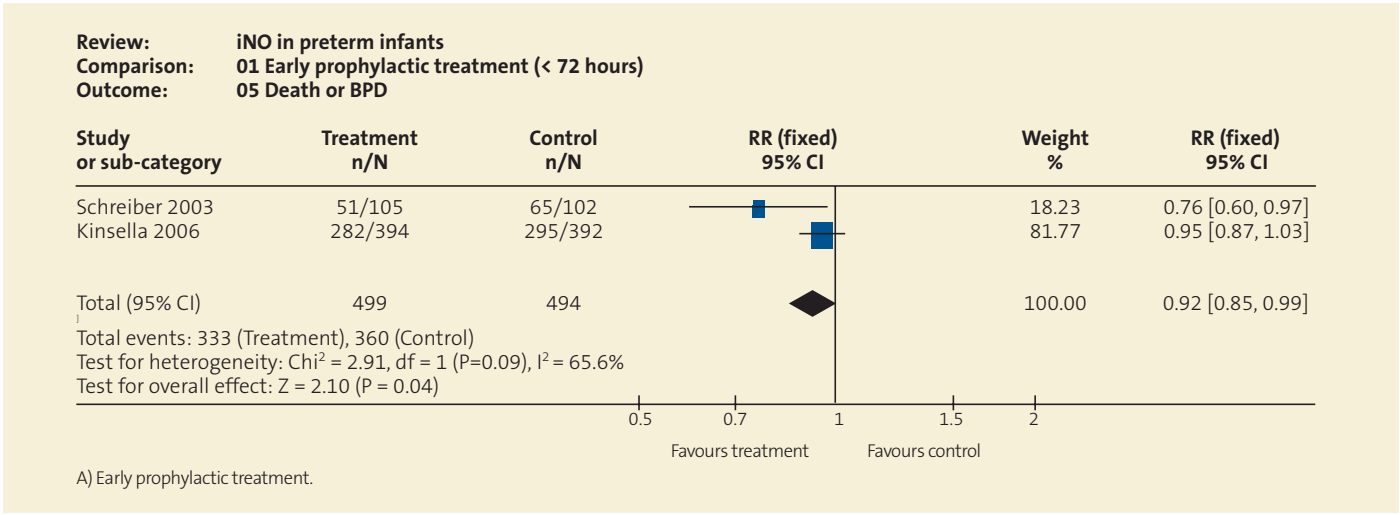
TABLE 4 Meta-analyses of randomised controlled trials of iNO in preterm babies: Overview of outcomes.

echocardiographic confirmation of extrapulmonary shunting (i.e. PPHN). There is currently insufficient evidence to support the routine use of iNO in babies with congenital diaphragmatic hernia[23].

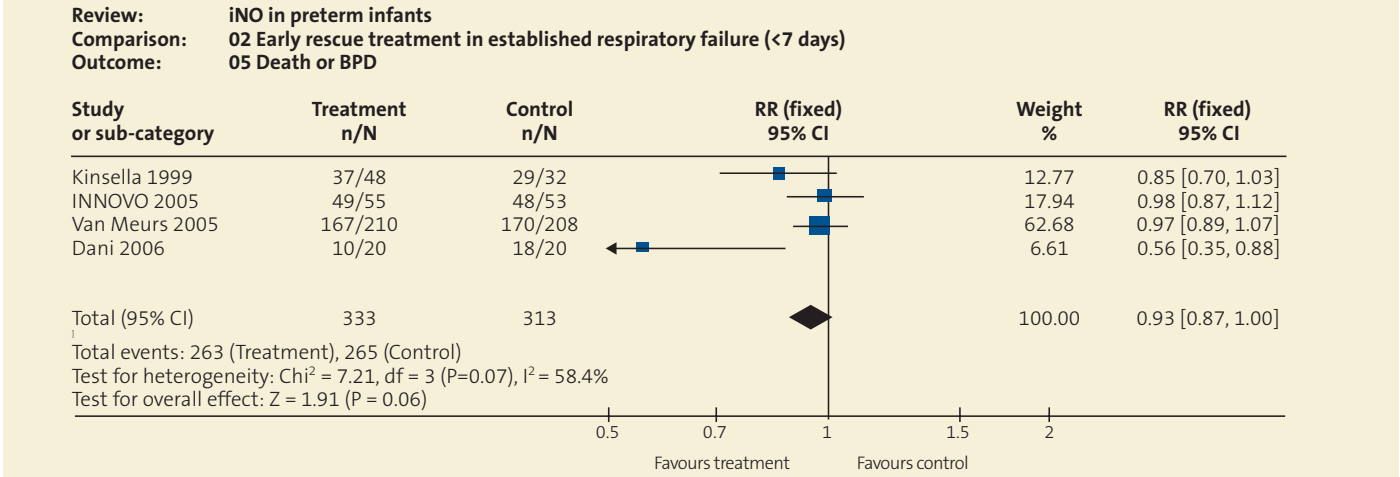
Preterm infants

The use of iNO in preterm infants remains controversial. Some experts would argue that iNO should only be used in preterm infants in the context of a randomised controlled trial. Although there is little evidence to support its use routinely in preterm babies with established respiratory failure, the majority of units in the UK are currently treating preterm babies with iNO. The authors' own practice is to restrict iNO therapy to a sub-group of preterm babies with moderately-severe respiratory failure (OI > 15) in whom extrapulmonary shunting has been confirmed on echocardiography.

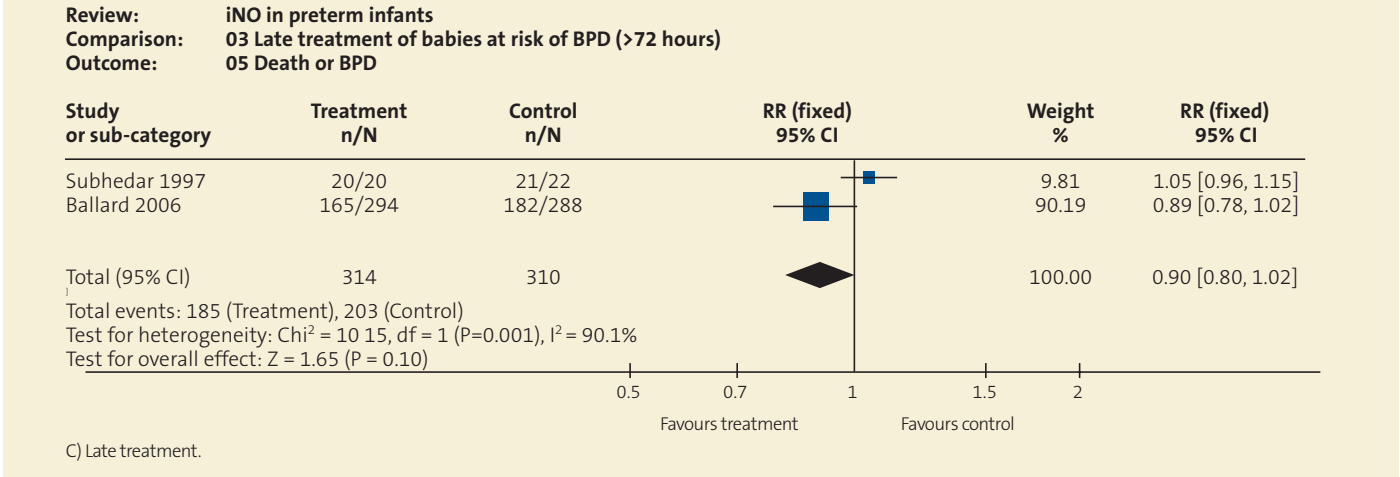
The early 'prophylactic' use of iNO in ventilated preterm babies is an approach with encouraging preliminary results, but there is currently insufficient evidence to support this practice as part of routine clinical management. Specifically, adequate information about long term neurodevelopmental outcomes is not available in this group of babies. Similarly, there is little convincing evidence to suggest that late treatment with iNO is safe and effective in



A) Early prophylactic treatment.



B) Early rescue treatment in established respiratory failure. BPD and Death/BPD were not reported in the study by Srisuparp et al[15].



C) Late treatment.

FIGURE 2 Meta-analyses of randomised controlled trials of iNO in preterm babies: Death or BPD in infants treated with iNO versus controls.

improving outcomes in ventilator-dependent babies at risk of death/BPD.

What is the optimal dose of iNO?

Most studies have used doses of 2-20 ppm of iNO although some have used higher doses, up to 80 ppm. There are very few randomised controlled trials that have directly compared the safety and efficacy of different doses of iNO.

Term and near-term infants

A starting dose of 10-20 ppm iNO was associated with a better short term oxygenation response compared to a lower starting dose of 1-2 ppm in a small RCT of 36 mature neonates with hypoxic respiratory failure[24]. Treatment with iNO at 2 ppm for one hour did not significantly improve oxygenation in hypoxaemic neonates, but subsequently reduced the clinical response to 20 ppm[25]. Two dose-response studies have suggested that the oxygenation response to iNO was similar

when doses of 5 to 80 ppm iNO were compared in a group of term and near-term neonates[4, 26]. Babies who fail to respond to 20 ppm are very unlikely to respond to 80 ppm of iNO[1].

Preterm infants

One small RCT in preterm infants with respiratory distress syndrome found no evidence of benefit in short term oxygenation of treatment with 20 ppm versus 5 ppm iNO[27]. Three small dose response studies have been conducted in preterm infants. Whereas two studies reported no significant differences in oxygenation response to 1-20 ppm and 5-40 ppm[28-29], the third study found that only 21% of preterm babies who responded to iNO did so at 10 ppm, with the remainder responding to higher doses of 20 or 40 ppm[30]. However, in the authors' experience, preterm babies not responding to 20 ppm almost never respond to higher doses.

It is likely that a baby's response to iNO will depend more on individual factors (such as the underlying diagnosis, haemodynamic status and effectiveness of delivery of iNO to the terminal air spaces) than on the dose of iNO used. In the absence of convincing evidence to support the use of one dose over another, it seems prudent to limit the exposure to iNO by using the lowest effective dose. The maximum dose of iNO in term and preterm neonates should be limited to 20 ppm. One of two approaches is commonly used in clinical practice, either:

- start with a low dose (e.g. 5 ppm) and increase in steps until no further improvement in oxygenation is observed or
- start at the maximum recommended dose (e.g. 20 ppm) and wean to the lowest dose tolerated without deterioration in oxygenation.

Factors affecting response to iNO

Between one-third and one-half of babies treated with iNO fail to respond, or only have a partial response. Short-term oxygenation response is related to underlying diagnosis, radiographic severity of lung disease and the presence of an extra-pulmonary shunt[31-33]. Babies who show the best response to iNO are those with relatively clear lung fields on chest X-ray and/or documented extrapulmonary shunt on echocardiography. The oxygenation response is greater in babies with primary PPHN than those with secondary PPHN.

Toxicity

Most studies have shown that the complications of iNO therapy are rare at doses < 20 ppm. Higher doses may be associated with methaemoglobinaemia and/or build up of nitrogen dioxide. Babies treated with iNO have not been shown to be at increased risk of other potential complications such as pulmonary haemorrhage, intracranial haemorrhage or systemic hypotension.

How and when should iNO be weaned and discontinued?

The typical duration of iNO therapy in clinical trials has been less than 5 days although there is little consensus with regard to the threshold and timing for weaning and/or discontinuing iNO therapy. Furthermore, few studies have addressed the optimal method of weaning and/or stopping iNO therapy.

The practice in the authors' unit is to commence weaning iNO once the FiO_2 < 0.70. The dose of iNO should be initially weaned in stepwise fashion, for example, in steps of 5 ppm from 20 ppm to 5 ppm, and then in steps of 1 ppm, until a final dose of 1 ppm, before finally stopping iNO therapy[34]. The greatest fall in oxygenation occurs during final discontinuation of therapy, as opposed to during any of the steps of the weaning phase[35]. Babies who fail to tolerate discontinuation of iNO therapy should continue on low dose iNO (1 ppm) for a further 12-24 hours before another attempt at discontinuation is made.

Summary

Inhaled nitric oxide is an effective treatment for term and near-term babies with hypoxaemic respiratory failure. Randomised controlled trials have consistently demonstrated an improvement in oxygenation and a reduction in the need for ECMO, without an excess of short or long term adverse effects.

Data from RCTs have failed to demonstrate clear evidence supporting the use of iNO routinely in preterm infants. The most encouraging reports come from studies in which iNO has been used as an early 'prophylactic' treatment to prevent death or BPD. Further studies will need to define more clearly whether this approach is associated with better long term (as well as short term) outcomes, and determine which patient and disease characteristics are best suited to iNO therapy.

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